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GUIDELINES FOR RADIOPHARMACEUTICAL QUALITY ASSURANCE IN NUCLEAR MEDICINE

Canada

GUIDELINES FOR RADIOPHARMACEUTICAL QUALITY ASSURANCE IN NUCLEAR MEDICINE

Drugs Programme
Health Protection Branch

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FOREWORD

These guidelines were originally published in 1982 as Environmental Health Directorate Publication 82-EHD-77. They were revised in 1988 to reflect the Health Protection Branch's position concerning hospitals and clinics that manufacture Schedule C drugs (radiopharmaceuticals, kits for the preparation of radiopharmaceuticals, radionuclide generators), and to assist these facilities in establishing and operating a radiopharmaceutical quality assurance programme.

This current revision incorporates recommendations made by the National Advisory Committee on Radiopharmaceutical Quality Assurance in Nuclear Medicine, which was formed in 1989. The committee represents all specialties in nuclear medicine, as its membership is drawn from the following national organizations:

Canadian Association of Nuclear Medicine

Canadian Association of Radiopharmaceutical Scientists

Canadian Organization of Medical Physicists

Canadian Society of Hospital Pharmacists

Canadian Association of Medical Radiation Technologists

The terms of reference of the committee are:

-to review the Health Protection Branch Guidelines for Radiopharmaceutical Quality Assurance in Nuclear Medicine and to make recommendations in keeping with current practices;

-to provide advice on current radiopharmaceutical practices and problems that the inspection program has identified; and

-to report to the Assistant Deputy Minister (or designate), Health Protection Branch.

The extent of involvement of nuclear medicine personnel in radiopharmaceutical preparation will dictate the degree of quality assurance that must be exercised to ensure the safety and efficacy of an administered Schedule C drug. This document outlines minimum quality assurance requirements for various operations. Facilities that are subject to licensing under the *Food and Drugs Act* are beyond the scope of this document.

These guidelines are neither exhaustive nor inflexible, and they may not cover every possible situation. Within the framework provided, they may need to be adapted according to the specific requirements of some radioactive drugs.

The Drugs Programme may revise these guidelines, if required, so that they continue to reflect current radiopharmaceutical quality assurance practices. Comments and suggestions for future revisions will be welcomed.

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INTRODUCTION

These guidelines have been prepared to help hospitals and nuclear medicine clinics establish and operate radiopharmaceutical quality assurance programs. They may also serve as a reference for medical ethics committees that evaluate medical research proposals to use licensed radiopharmaceuticals in humans. Use of unlicensed radiopharmaceuticals for medical research is beyond the scope of this document.

In general, radiopharmaceutical activities in hospitals and clinics involve one or more of the following:

-procuring unit doses, generally technetium-99m-labelled radiopharmaceuticals, from a licensed centralized radiopharmacy service;

-dispensing individual patient doses of a commercially supplied radiopharmaceutical from a multi-dose container;

-reconstituting commercially available radiopharmaceutical kits using generator-produced technetium-99m or other sterile, apyrogenic radiopharmaceuticals;

- radiolabelling of blood cells.

In the opinion of the Health Protection Branch, hospitals and clinics that follow these guidelines are in compliance with the manufacturing requirements of Section 12 of the *Food and Drugs Act* and Division 3 of the *Food and Drug Regulations*.

This document outlines minimum quality assurance requirements for the four activities listed above.

QUALITY ASSURANCE OF INDIVIDUAL PATIENT DOSES OF A COMMERCIALLY PROCURED RADIOPHARMACEUTICAL

Commercially distributed final-dosage-form radiopharmaceuticals are licensed under the *Food and Drugs Act*. Hence, the manufacturer is responsible for these products' radionuclidic purity, radiochemical purity, sterility, apyrogenicity, particle size, pharmaceutical elegance and other acceptance criteria. When a product released for sale does not meet the above acceptance criteria, the user must advise the manufacturer. The manufacturer must evaluate the situation, take corrective action and, if necessary, advise the Drugs Programme immediately.

Commercially distributed radionuclides labelled "Radiochemical" should not be administered to humans. A radiochemical is not pharmaceutical grade and may not have been adequately safety tested.

Alteration of a manufacturer's final product or instructions contravenes federal legislation and the conditions contained in the manufacturer's Notice of Compliance. The user must follow the manufacturer's storage recommendations for the radiopharmaceutical, and take the following quality control steps.

1. Radionuclide (Dose) Calibrator Quality Control

Two good references for acceptable testing and routine quality control are (1) *Quality Control of Nuclear Medicine Instruments*, IAEA, Technical Document 602, International Atomic Energy Agency, Vienna, 1991 and (2) *American National Standard Calibration and Usage of 'Dose Calibrator' Ionization Chambers for the Assay of Radionuclides*, American National Standards Institute (ANSI) N42.13-186-1986 [available in Canada from: Standards Council of Canada, 45 O'Connor Street, Suite 1200, Ottawa, Ontario K1P 6N7, telephone: (613) 238-3222]. The radionuclide calibrator manual should also be checked for appropriate operating procedures. Note that quality control recommendations in this guideline may differ from those quoted in the manufacturer's manual or from those endorsed by other countries or organizations.

a)All instruments are geometry-dependent with respect to container

material, container size and shape (vial versus syringe), volume contained and position within the ionization chamber. Therefore, these parameters should be carefully studied when a new unit is put into service or a new container is used.

b)Linearity of response over the anticipated range of activities should be verified at least semi-annually. All radionuclide calibrators that use a battery will give a reduced reading at high activity values when the battery begins to fail. This may result in patients receiving higher doses of radiation than intended. If a radionuclide calibrator has a voltage "test" button, this should be used daily to determine constancy of voltage.

Suggested linearity test procedure for technetium-99m:*

i)select an activity of technetium-99m that is twice the highest patient dose;

ii)measure this activity over a two-day period (e.g. 0, 4, 8, 24, 30, 48 hours);

iii)plot the results on semi-log paper. Decay-correct the lowest value obtained back to the start of the study. The line between the theoretical initial value and the lowest value will represent the theoretical decayed activity plot; and

iv)observe the difference between the theoretical and actual readings. A deviation of ± 5% or more from the theoretical decayed activity indicates that the equipment may need servicing.

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* Alternatively, the lead sleeve shielding system, which consists of a series of attenuating lead tubes, may be used, provided the initial test is validated using the decay method.

c)Radionuclide calibrators should be checked daily for satisfactory performance using at least one suitable check source, and a permanent record should be maintained. Preferably, this record should be maintained as both a log book and a graph with control lines that represent ± 5% of the theoretical decayed activity. The latter often reveals a gradual instrument drift that might not be noticed if only a log book is used.

The same check source should be measured once a week on all other relevant radionuclide settings (Tc-99m, Ga-67, Tl-201, I-131, etc.) and these readings should be documented. Such measurements will verify the uniformity of response of specific radionuclide calibrator settings.

d)Daily background readings should also be recorded and then monitored throughout the day. Increased background may be due to a contaminated ionization chamber or an inadequately shielded radioactive source within the laboratory.

e)Initial calibrations should be confirmed upon receipt of a new instrument or if the response of the secondary check source has changed, as may happen after instrument repair, for example. The manufacturer's certificate of calibration should be available as a reference, should repairs be required. Following any repairs, documentation should be provided to show that the instrument has been tested with a certified check source. All check sources should be traceable to a primary standard issued by the National Institute of Standards and Technology (NIST). The National Research Council of Canada (NRC) offers a calibration service*, which can be a useful addition to the radionuclide calibrator quality assurance program.

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* The NRC Calibration Service for Radionuclide Calibrators in Canadian Hospitals, Institute for National Measurement Standards, National Research Council of Canada, Ottawa, Ontario K1A 0R6; telephone: (613) 993-2197.

2. Visual Inspection of Product

Visual inspection not only ensures the absence of foreign matter (i.e. coring of the rubber stopper in multi-dose vials), but also helps to establish product identity by confirming whether the product is a solution, a colloid or a macroaggregated suspension.

It is also important to verify the labelling information to ensure that the correct product, volume and activity has been provided.

3. Verification of Each Patient Dose

Whether the radiopharmaceutical is procured as a unit dose from a licensed radiopharmacy or withdrawn from a multi-dose vial, it should be assayed in a radionuclide calibrator and visually inspected. The results of these observations must be recorded. The assay verifies the amount of radioactivity that is present and also serves as a partial check for radionuclidic identity. If the radionuclide calibrator response is different from the expected response (± 10%), this may indicate an incorrect radionuclide or a mislabelled product. These results should be investigated further.

Dose verification applies to therapeutic as well as diagnostic radiopharmaceuticals. All radiopharmaceutical products should be double-checked for labelling and dose calculations. This is particularly important for radiopharmaceuticals that contain beta-emitting radionuclides because radionuclide calibrator measurements may be inaccurate for these radionuclides.

4. Record Keeping

a)Records of the lot numbers and manufacturers of kits and diluents should be maintained.

b)Records identifying patients, actual doses dispensed and personnel responsible for preparation, testing and dispensing should also be maintained. Nuclear medicine departments should also be aware of the current requirements of the Canadian Council on Health Services Accreditation [1730 St. Laurent Blvd., Suite 430, Ottawa, Ontario, K1G 5L1; telephone: (613) 738-3800] regarding record keeping.

c)A separate file should be maintained to record product-related problems.

d)All adverse drug reactions and altered biodistributions should be reported to the manufacturer and the Drugs Programme (see sample reporting form in Appendix I).

e)As indicated in the *Food and Drug Regulations*, all drug records should be kept for two years after product expiry; however, the requirements of other regulatory agencies may be different. Records of product-related problems and adverse drug reactions or altered biodistributions should be kept for five years.

QUALITY ASSURANCE OF RADIOPHARMACEUTICALS PREPARED FROM COMMERCIALLY AVAILABLE KITS AND GENERATORS

Sales of kits for preparing radiopharmaceuticals, as well as sales of radionuclide generators and radiopharmaceuticals, are subject to the licensing requirements of the *Food and Drugs Act* and *Regulations*. The manufacturer is responsible for ensuring the safety and efficacy of its products.

Hospitals and clinics manufacturing radiopharmaceuticals using radionuclide generators, radiopharmaceuticals and kits obtained from licensed manufacturers are responsible for the quality of the radioactive drug, since their personnel prepare the final dosage form that is administered to the patient. In the opinion of the Health Protection Branch, hospitals and clinics will comply with Section 12 of the *Food and Drugs Act* and Division 3 of the *Food and Drug Regulations* if they follow these guidelines pertaining to radiochemical purity testing; monitoring technetium-99m generator eluates for molybdenum-99 and aluminum contamination; final product radioactivity assays and related instrument calibrations; periodic retrospective sterility tests; adherence to manufacturers' recommendations concerning instructions for preparation, storage requirements and useful lifetimes; and adequate record keeping.

During preparation, the following factors will contribute to the quality and, hence, the efficacy of the radiopharmaceutical:

-careful adherence to the manufacturer's instructions for product preparation;

-use of sodium pertechnetate Tc-99m solutions free of oxidants;

-use of bacteriostatic-free saline for elution and dilution purposes;

-use of a specifically recommended manufacturer's radiopharmaceutical (such as indium-111 chloride) for certain kits;

-visual inspection of the prepared radiopharmaceutical to ensure absence of foreign matter;

-maintenance of precautions to ensure sterility; and

-adherence to recommended storage conditions and expiration times for both the kit and the final radiolabelled product.

Radionuclides labelled as "Radiochemical" should not be used in preparing radiopharmaceuticals intended for human use. A radiochemical is not pharmaceutical grade and may not have been adequately safety tested.

The minimum quality control steps recommended for departments that prepare radiopharmaceuticals, as defined in this section, follow.

1. Radionuclide (Dose) Calibrator Quality Control

Two good references for acceptable testing and routine quality control are (1) *Quality Control of Nuclear Medicine Instruments*, IAEA, Technical Document 602, International Atomic Energy Agency, Vienna, 1991 and (2) *American National Standard Calibration and Usage of 'Dose Calibrator' Ionization Chambers for the Assay of Radionuclides*, American National Standards Institute (ANSI) N42.13-186-1986 [available in Canada from: Standards Council of Canada, 45 O'Connor Street, Suite 1200, Ottawa, Ontario K1P 6N7, telephone: (613) 238-3222]. The radionuclide calibrator manual should also be checked for appropriate operating procedures. Note that quality control recommendations in this guideline may differ from those quoted in the manufacturer's manual or from those endorsed by other countries or organizations.

a)All instruments are geometry-dependent with respect to container material, container size and shape (vial versus syringe), volume contained and position within the ionization chamber. Therefore, these parameters should be carefully studied when a new unit is put into service or a new container is used.

b)Linearity of response over the anticipated range of activities should be verified at least semi-annually. All radionuclide calibrators that use a battery will give a reduced reading at high activity values when the battery begins to fail. This may result in patients receiving higher doses of radiation than intended. If a radionuclide calibrator has a voltage "test" button, this should be used daily to determine constancy of voltage.
Suggested linearity test procedure for technetium-99m:*

i)obtain an activity of at least 37 GBq (1 Ci) of sodium pertechnetate Tc-99m;

ii)measure the source on the Tc-99m setting for three to four days (e.g. 0, 6, 24, 30, 48, 54, 72, 80, 96 hours);

iii)plot the readings on semi-log paper. Decay-correct the lowest value obtained back to the start of the study. The line between the theoretical initial value and the lowest value will represent the theoretical decayed activity plot; and

iv)observe the difference between the theoretical and actual readings. A deviation of ± 5% or more from the theoretical decayed activity indicates that the equipment may need servicing.

c)Radionuclide calibrators should be checked daily for satisfactory performance using at least one suitable check source, and a permanent record should be maintained. Preferably, this record should be maintained as both a log book and a graph with control lines that represent ± 5% of the theoretical decayed activity. The latter often reveals a gradual instrument drift that might not be noticed if only a log book is used.

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*Alternatively, the lead sleeve shielding system, which consists of a series of attenuating lead tubes, may be used, provided the initial test is validated using the decay method.

The same check source should be measured once a week on all other relevant radionuclide settings (Tc-99m, Ga-67, Tl-201, I-131, etc.) and these readings should be documented. Such measurements will verify the uniformity of response of specific radionuclide calibrator settings.

d)Daily background readings should also be recorded and then monitored throughout the day. Increased background may be due to a contaminated ionization chamber or an inadequately shielded radioactive source within the laboratory.

e)Initial calibrations should be confirmed upon receipt of a new instrument or if the response of the check source has changed, as may happen after instrument repair, for example. The manufacturer's certificate of calibration should be available as a reference, should repairs be required. Following any repairs, documentation should be provided to show that the instrument has been tested with a certified check source. All check sources should be traceable to a primary standard issued by the National Institute of Standards and Technology (NIST). The National Research Council of Canada (NRC) offers a calibration service*, which can be a useful addition to the radionuclide calibrator quality assurance program.

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* The NRC Calibration Service for Radionuclide Calibrators in Canadian Hospitals, Institute for National Measurement Standards, National Research Council of Canada, Ottawa, Ontario K1A 0R6; telephone: (613) 993-2197.

2. Technetium-99m Generator Quality Control

Manufacturers of technetium-99m generators are required to monitor generator eluates to ensure compliance with the radionuclidic impurity limits stipulated in the *Food and Drug Regulations* (Table 1).

Table 1. Maximum Permissible Impurities in Technetium-99m ***(at Time of Injection)***

Reference: *Food and Drug Regulations*, C.03.204.(2)

RADIONUCLIDE	QUANTITY	
	μCi/mCi	kBq/MBq
Gamma Emitters		
Molybdenum-99	0.03	0.03
Ruthenium-103	0.05	0.05
Iodine-131	0.01	0.01
Iodine-132	0.75	0.75
Cesium-134	0.01	0.01
All other gammas	0.01	0.01 (total)
Beta Emitters		
Strontium-89	6×10^{-4}	6×10^{-4}
Strontium-90	1.5×10^{-5}	1.5×10^{-5}
All Alpha Emitters	1.0×10^{-7}	1.0×10^{-7} (total)

a) Molybdenum-99 Breakthrough

The *Food and Drug Regulations'* allowable limit for molybdenum-99 is 0.03 kBq Mo-99/MBq Tc-99m (0.03 μCi Mo-99/mCi Tc-99m) at time of administration of the technetium-99m. Eluates should be monitored for the level of molybdenum-99 contamination each time a generator is eluted, and decay-corrected to time of administration. A change in generator performance characteristics or damage in transit may cause significant molybdenum-99 to be eluted from a generator. Instructions for checking molybdenum-99 content in the eluate may be found in some generator manufacturers' package inserts. Some instrumentation may not be adequately sensitive to detect the limit specified in the *Food and Drug Regulations*. In this case, each institution must develop its own methodology for molybdenum-99 assay. A significant molybdenum-99 breakthrough, which would cause substantial unnecessary patient exposure if administered, should be readily detected.

b) Aluminum Breakthrough

Aluminum contamination in the generator eluate should also be checked, at least on the first elution, to ensure that it is below the *United States Pharmacopeia's (published by USPC Inc., Rockville, MD)* limit of 10 μg/mL. Excessive aluminum levels may adversely affect the quality of the final product.

3. Visual Inspection of Product

Visual inspection of the prepared radiopharmaceutical not only ensures the absence of foreign matter (i.e. coring of the rubber stopper), but also helps to establish product identity by confirming whether the product is a solution, a colloid or a macroaggregated suspension.

4.Radiochemical Purity

The radiochemical purity of prepared radiopharmaceuticals should be monitored before they are administered to patients. The following factors may affect radiochemical purity and, hence, product efficacy:

a)purity of the radiopharmaceutical (e.g. technetium-99m generator eluate, indium-111 chloride, etc.) used to reconstitute the vial contents;

b)loss of vacuum or inert atmosphere from the reaction vial due to improper sealing. Presence of air in the vial may result in inadequate levels of the reducing agent, such as stannous ion, or may affect the level of the active ingredient;

c)non-adherence to the kit manufacturer's reconstitution instructions; and

d)subtle changes in the manufacturer's production sequence that may not be evident from initial quality control release tests but that may affect long-term stability.

Radiochemical purity testing procedures that are reasonably rapid and adaptable to a nuclear medicine setting are documented in the literature and are available from manufacturers. Clear, easy-to-follow descriptions of test methods should be readily available to all staff. The *United States Pharmacopeia* now includes monographs on many radiopharmaceuticals, that discuss methods for testing radiochemical purity. The acceptability of prepared radiopharmaceuticals may be confirmed by reference to the specifications quoted in either these monographs or those of other recognized pharmacopoeiae. Kit manufacturers generally test their products for compliance with these pharmacopoeial requirements.

A substandard preparation may still yield an acceptable scan. However, in some cases, a scan may have to be repeated with another preparation. In both instances, the patient would have received an avoidable and unnecessary radiation exposure.

5. Verification of Macroaggregate Particle Size

The particle size of radiolabelled macroaggregates should be verified prior to use. The clinician remains responsible for the final product and for the number of particles injected.

6.Labelling

Radiopharmaceuticals should be labelled with adequate identifying information to prevent errors during preparation, storage and use.

7. Verification of Each Patient Dose

Since variable amounts of radioactivity may be added to a reaction vial and one or more doses withdrawn from it, the radioactivity content of each patient dose should be verified and documented prior to administration, using a properly standardized radionuclide calibrator. The assay verifies the amount of radioactivity that is present and also serves as a partial check for radionuclidic identity. If the radionuclide calibrator response is different from the expected response
(± 10%), this may indicate an incorrect radionuclide or a mislabelled product. These results should be investigated further.

8.Microbiological Controls

Manipulations involving kits and generators take place within closed systems (vial-syringe combinations). However, radiopharmaceuticals prepared from kits do not generally contain preservatives, and consequently the pH and saline environment may support microbial growth. Retrospective sterility tests should be conducted on randomly selected batches of product to check the adequacy of aseptic technique. These tests should be conducted monthly, and weekly for the first month when new personnel are involved. Sterility tests should be performed according to test

methodology described in the current edition of the *United States Pharmacopeia*.

Good pharmaceutical practices dictate that audits of aseptic technique should be performed by an appropriate peer.

9.Record Keeping

a)Quality control test results and records of the lot numbers and manufacturers of kits, generators and diluents used should be maintained.

b)Records identifying patients, actual doses dispensed, and personnel responsible for preparation, testing and dispensing should also be maintained. Nuclear medicine departments should also be aware of the current requirements of the Canadian Council on Health Services Accreditation [1730 St. Laurent Blvd., Suite 430, Ottawa, Ontario, K1G 5L1, telephone: (613) 738-3800] regarding record keeping.

c)A separate file should be maintained to record product-related problems.

d)All adverse drug reactions and altered biodistributions should be reported to the manufacturer and the Drugs Programme (see sample reporting form in Appendix I).

e)As indicated in the *Food and Drug Regulations*, all drug records should be kept for two years after product expiry; however, the requirements of other regulatory agencies may be different. Records of product-related problems and adverse drug reactions or altered biodistributions should be kept for five years.

CELL RADIOLABELLING PRACTICES IN AN OPEN SYSTEM

Cell radiolabelling procedures require that blood be withdrawn from the patient and, after the appropriate manipulations, reinjected into the patient. Because blood products can transmit infection, it is essential that universal safety precautions be adhered to when cell manipulations are performed. These manipulations are performed on an individual patient's blood, so care must also be taken to ensure that the blood sample or separated cells do not become contaminated. Nuclear medicine technologists and radiopharmacists performing cell radiolabelling must have appropriate training in safe cell-handling practices.

All cell radiolabelling procedures should be performed in an aseptic environment to protect the laboratory worker and ensure that blood does not become contaminated.

Standards for Transfusion Medicine should be followed (see below):

1. A positive identification of the patient must be made before drawing the blood specimen or reinjecting blood.

2. Written patient consent must be obtained.

3. The blood must be labelled "For Autologous Use Only". The label must also show the name of the patient and include other appropriate identifying information such as the patient identification number.

4. The sterility of the blood and components shall be maintained during processing by use of aseptic methods and sterile pyrogen-free equipment and solutions in a vertical laminar flow hood (Class II, Type B2). A maintenance schedule shall be in place for the laminar flow hood.

5. Only personnel trained in aseptic technique and cell radiolabelling procedures shall be permitted to carry out the procedure. Training must be documented.

6. Only one patient sample shall be processed at a time to guard against cross contamination and confusion among specimens.

7. When possible, patients' blood shall be tested for transmissible diseases (such as hepatitis B or C, HIV and syphilis) before being processed.

8. A standard operating procedure (SOP) describing the steps in the radiolabelling procedure must be developed and followed. A control record outlining all steps in the labelling procedure, including reagents, their lot numbers and the signature of the responsible personnel, shall be used to document all pertinent information relating to the labelling procedure.

9. Processed cells should be reinjected into the patient within four hours, and no later than six hours, from the time the blood was drawn.

10. During reinfusion, recipients must be monitored by a physician. Use of microaggregate filters during reinfusion is recommended to prevent cell aggregates from being injected. Use of a 19-gauge or larger needle is required to prevent hemolysis in the case of red blood cells.

Further details on appropriate cell radiolabelling practices may be obtained from the following two references:

Zabel, P., N. Robichaud and A. Hiltz. Facilities and Equipment for Aseptic and Safe Handling of Blood Products. *J Nucl Med Technol*, December 1992, 20(4): 236-241.

Zabel, P., N. Robichaud and A. Hiltz. Personnel and Product Protection During Manipulation of Blood Products. *J Nucl Med Technol*, March 1993, 21(1): 33-37.

Further details on appropriate cell storage, handling and transfusion practices may be obtained from the following reference:

Standards for Transfusion Medicine, 4th Edition, Canadian Society for Transfusion Medicine. 1991. (Available from the Canadian Society for Transfusion Medicine, Treasurer, P.O. Box 3028, Saskatoon, Saskatchewan S7K 3S9).

DEVIATIONS FROM MANUFACTURER'S INSTRUCTIONS

Alteration of a manufacturer's final product or instructions contravenes federal legislation and the conditions contained in the manufacturer's Notice of Compliance.

1. Endotoxin Levels

The endotoxin limit for intrathecally administered radiopharmaceuticals is 14 U.S.P. E.U. per dose, compared to 175 U.S.P. E.U. per dose for intravenously administered radiopharmaceuticals. Manufacturers that market radiopharmaceuticals intended and approved only for intravenous use will not guarantee the stricter endotoxin levels required for intrathecal use. Only a limulus amoebocyte lysate test performed on the final injectable product by qualified personnel prior to administration can be used to determine the endotoxin level in the product.

2. Dilutions and Compatibility

It is important to be aware of manufacturers' guidelines when performing dilutions. If dilutions are performed, compatibility of the drug with the diluent (radiochemical purity, visual inspection, etc.) and the possibility of adsorption must be investigated. Compatibility studies should also be performed if the radiopharmaceutical is stored in a syringe for a long time before being administered to the patient. This will ensure that the radiopharmaceutical is not interacting with, or being degraded by, the syringe or needle components in contact with it. Any diluent such as saline, including saline stored in bags or bottles, must not be used for longer than eight hours. Records of dilution volumes, lot numbers and suppliers of diluents should be maintained, along with the radiopharmaceutical receipt and usage records. Nuclear medicine staff may require some expert assistance to establish adequate quality control tests.

CONCLUSIONS

Patients undergoing nuclear medicine procedures must be assured that the drugs they receive are safe and efficacious, no matter where these drugs are manufactured. Conscientious adherence to the recommendations presented in this document will help to ensure that radiopharmaceuticals satisfy these requirements.

Questions concerning interpretation of any part of these guidelines should be referred to:

Radiopharmaceutical Division
Bureau of Biologics and Radiopharmaceuticals
Drugs Programme
Building 6
Address Locator: 0603C4
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

Telephone: (613) 954-6704
Facsimile: (613) 941-5841

APPENDIX I - DRUG PROBLEM REPORTING PROGRAM

Problem Noted or Suspected

Adverse reaction .....Altered biodistribution .....

Defective product.....

Other . .....

Date of incident.....

Has the manufacturer been informed? YES / NO

Complete the pertinent sections below.

Patient Information

1.Patient (initials).....Hospital no. .....
Age. . . . Sex .....Date of study.. ....

Nature of study

....
....

Clinical diagnosis

....
....

2.Nature of reaction (timing, symptoms and clinical observations)

....
....
....
....

Does the patient have any known allergies, etc.?

.....
.....
.....
.....

3.Other medications currently or recently taken (including over-the-counter drugs, e.g. antacids)

.....
.....
.....
.....
.....

4.Treatment of reaction (drugs and resuscitative measures required)

.....
.....
.....
.....
.....

5.Any other comments

.....
.....
.....
.....
.....

6.Outcome

.....
.....
.....
.....
.....

Radiopharmaceutical

1. Product name (e.g. Tc-99m pentetate)

.....

Central radiopharmacy name (if applicable)

....

2. Complete the following section(s):

a) Kit - Manufacturer ....
Lot no. .....Activity..... ....Volume..... ....
b) Radionuclide generator - Manufacturer ....
Size .....Lot no. ....

c) Quality control - Mo^{99} breakthrough ....
Aluminum breakthrough ....

d) Other - Manufacturer ....
Lot no. .....Activity..... ....Volume..... ....
Cal. time/date ....Expiry. ....

3. Defect noted

- Transport damage
- Radionuclidic purity
- Label error
- pH
- Package insert
- Elution efficiency
- Appearance
- Particulate contamination
- Rad. surface contamination
- Biodistribution
- Radioactive concentration
- Sterility
- Total radioactivity
- Pyrogens
- Radiochemical purity
- Other .....

4. Detailed description of problem

.....
.....
.....
.....
.....

5. Test(s), if any (include ITLC data, particle size, etc.), performed to confirm problem

.....
.....
.....
.....
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6. Any relevant clinical details of patient(s)

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7. Action taken

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8. Outcome

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Signed .....
Name .....
Address .....
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Telephone.....
Facsimile .....

Confidentiality

Details will not be disclosed without the express permission of the person submitting this report.

Please return this completed form to Radiopharmaceuticals Division, Bureau of Biologics and Radiopharmaceuticals, Address Locator: 0603C4, Tunney's Pasture, Ottawa, Ontario K1A 0L2, Facsimile: (613) 941-5841.